Remarks

The Applicants address the Examiner's remarks in the order he presented them.

Information Disclosure Statement

The Examiner stated that he did not review DE 100 33 195 A1 and DE 34 30 556 A1 because "these references are not present in the instant application." The Applicants submit with this Amendment a new Information Disclosure Statement citing PCT Patent Application Publication No. WO 02/04486, which corresponds to DE 100 33 1950 A1. The Applicants submit DE 34 30 556 along with the abstract the European Patent Office provides with its listing of the application on-line (http://ep.espacenet.com/).

Title of the Invention

The Examiner required a new title. The Applicants have deleted the original title and replaced it with the title the Examiner suggested.

Use of Trademarks

The Applicants respectfully note the Examiner's admonition regarding the use of registered trademarks.

The Rejection Under § 112, second paragraph

The Examiner rejected claims 1-2 and 7-20 under 35 U.S.C. § 112, second paragraph, stating that claim 1 is indefinite in its recitation of "a natural hirudin isoforms." The Applicants respectfully submit that their amendment to claim 1 satisfactorily addresses the Examiner's rejection.

As to claim 16, the Examiner stated that it is "unclear where the step of separating the fermentation supernatant from the host cell is to occur." The Applicants respectfully submit that their amendment to claim 16 satisfactorily addresses the Examiner's rejection.

As to claim 17, the Examiner asked whether the limitation "removing the protein encoded by protein(Y) from the fusion protein" means "cleaving the protein encoded by protein(Y) from the fusion protein." The Applicants reply that it does not – that the specification and the context in which this limitation appears both make

clear that "removing" does not mean "cleaving." The Applicants respectfully submit that no amendment is necessary.

As to claim 20, the Examiner stated that the process of claim 14 is not limited to a process for production of insulin, but that claim 20 is indeed so limited. The Applicants respectfully submit that their amendment to claim 20 satisfactorily addresses the Examiner's rejection.

For the foregoing reasons, the Applicants respectfully request that the Examiner withdraw the rejection under § 112, second paragraph.

The Rejection Under § 112, First Paragraph

The Examiner rejected claims 1-2 and 7-20 under 35 U.S.C. § 112, first paragraph, stating that the specification discloses only three species of the genus of claimed nucleic acid sequences, i.e., the nucleic acid sequences obtained in Examples 1-3. As a result, the Examiner states, the claims do not comply with the written description requirement. The Applicants respectfully disagree.

The claims are directed to nucleic acid sequences of the formula P_x–S_x–B_n–(ZR)–Hir–(As_mR)–protein(Y)–T. It is a remarkable feature of the invention that "fusion proteins containing hirudin or hirudin derivatives at the N terminus can be exported from yeasts with good yields similar to those of hirudin itself," and that "hirudin is biologically active and mini-proinsulin is present in the correctly folded three-dimensional form . . . [so that] the protein of interest can be cleaved off directly and in active form." Application, at paragraph 0004. The Examiner objects that the claimed genus "encompasses species that are widely variant in structure." This is precisely correct, and it is also precisely the essence of the Applicants' invention: that as long as a nucleic acid sequence has the structure P_x–S_x–B_n–(ZR)–Hir–(As_mR)–protein(Y)–T, one of ordinary skill in the art will be able to select the proper components to encode a protein that "can be exported from yeasts with good yields similar to those of hirudin itself," such that "the protein of interest can be cleaved off directly and in active form."

The Examiner further objects that the specification, while being enabling for the nucleic acid sequences of Examples 1-3, does not enable the nucleic acid sequences as claimed. The Applicants respectfully disagree, for much of the same reasons they articulate above. The claims embody many species but one of ordinary

skill in the art will be able to identify species falling within the formula P_x–S_x–B_n–(ZR)–Hir–(As_mR)–protein(Y)–T that yield a desirable protein.

True, one might have to experiment to use the invention commensurately with its scope, as the claims, as amended, define it. But this does not defeat the claims. Experimentation is permitted; it may even be complex, MPEP § 2164.01, and may even be over an "extended period" or a "considerable amount," MPEP § 2164.06. The experimentation required here, whatever amount of it, is routine. One of ordinarily skill in the art, guided by the Applicants' formula P_x–S_x–B_n–(ZR)–Hir–(As_mR)–protein(Y)–T and the enabling examples of the specification, would have no difficulty carrying out such experimentation. The Applicants respectfully submit, therefore, that the specification comports with the enablement requirement.

For the foregoing reasons, the Applicants respectfully request that the Examiner withdraw the objection under § 112, first paragraph.

The Rejection Under § 102(b)

The Examiner rejected claims 1, 7-14, and 18-19 under 35 U.S.C. § 102(b), stating that Dawson *et al.* (U.S. Patent No. 5,434,073) anticipates them. The Applicants respectfully disagree.

The Dawson *et al.* reference does not disclose or suggest each and every element of the claims. Claim 1 requires a nucleic acid sequence of the structure P_x–S_x–B_n–(ZR)–Hir–(As_mR)–protein(Y)–T. The limitation B_n–(ZR) comprises 1-15 codons, when n is an integer from 1 to 15 (or a chemical bond, when n=0), Z is lysine or arginine, and R is arginine (or a chemical bond). The Examiner states that the Dawson *et al.* reference discloses an expression vector comprising Ser-Leu-Asp-Lys-Arg; the allegation, presumably, is that this sequence corresponds to B_n, when n = 3, and ZR, where Z is lysine and R is arginine. The expression vector of Dawson *et al.* does not contain this sequence, however.

The Dawson *et al.* reference discloses a method of preparing an expression vector that deletes from the final product the sequence the Examiner relies on. The expression vector of Dawson *et al.* comprises initially an α-factor pre-pro-peptide gene fused to the gene for epidermal growth factor (EGF). Col. 10, lns. 50-52. The EGF gene is subsequently removed by digestion with restriction endonucleases Hind III and Bam HI. Col. 10, lns. 58-60. The α-factor pro-peptide is then "rebuilt" with an

oligonucleotide adapter comprising Ser-Leu-Asp-Lys-Arg. Col. 10, ln. 58 – col. 11, ln. 5. But this sequence is then removed and replaced with Ile-Glu-Gly-Arg:

> [The] vector contains a ca. 465 bp KpnI DNA fragment which encodes a C-terminal portion of a first hirudin gene, a complete α-factor pre-pro-peptide sequence and the N-terminal portion of a second hirudin gene. In order to delete the α-factor pre-pro-peptide sequence and to insert DNA encoding a factor Xa-cleavable amino acid linker sequence (IEGR), the ca. 465 bp KpnI DNA fragment was transferred into a bacteriophage mutagenesis vector M13mp18.

Col. 12, lns. 54-62. In other words, the sequence the Examiner cites as corresponding to B_n(ZR) (Ser-Leu-Asp-Lys-Arg) is replaced with the sequence the Examiner cites as corresponding to As_mR (Ile-Glu-Gly-Arg). The vector of Dawson *et al.* therefore does not meet all of the limitations of the claims.

The above further shows that the expression vector of Dawson *et al.* does not comprise a nucleotide sequence in the order of the Applicant's vector, P_x–S_x–B_n–(ZR)–Hir–(As_mR)–protein(Y)–T. Order is relevant; it is a limitation of the claims. In the claimed vector, there is first B_n(ZR), then hirudin joined by As_mR to protein(Y). In the vector of the Dawson *et al.* reference, in contrast, there is hirudin first, joined by Ser-Leu-Asp-Lys-Arg to hirudin, and then the Ser-Leu-Asp-Lys-Arg is deleted and replaced by Ile-Glu-Gly-Arg. This is <u>not</u> the same as in the applicants' invention, as claimed, and is yet another reason why the vector of Dawson *et al.* does not meet all of the limitations of the claims.

For the foregoing reasons, the Applicants respectfully submit that the Dawson *et al.* reference does not disclose or suggest the invention of the claims, and respectfully request that the Examiner withdraw the rejection under § 102(b).

<u>The Rejection Under § 103(a)</u>

The Examiner rejected claims 15-16 under 35 U.S.C. § 103(a) over the Dawson *et al.* reference in view of Badziong *et al.* (U.S. Patent No. 5,095,092), and rejected claim 17 under § 103(a) over the Dawson *et al.* reference in view of Bischoff *et al.* The rejection is premised on obtaining fusion proteins according to the teachings of the Dawson *et al.*. Because Dawson *et al.* do not disclose the fusion proteins of the claimed invention, as argued above, the Applicants respectfully submit that combining the teachings of Dawson *et al.* with the teachings of Badziong

et al. or Bischoff *et al.* does not allow one to arrive at the claimed invention. The Applicants respectfully request that the Examiner therefore withdraw the rejection under § 103(a).

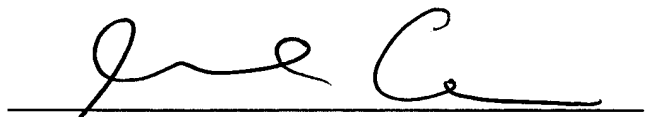
The Provisional Double Patenting Rejection

The Examiner provisionally rejected claim 1 under the doctrine of obviousness-type double patenting in view of claim 4 of U.S. Patent Application No. 10/076,634 and provisionally rejected claim 2 in view of U.S. Patent Application No. 10/076,631. The Applicants respectfully disagree, but for the time being merely note that the rejection is provisional.

Conclusion

The Applicants respectfully submit that the claims, as amended, are in condition for allowance, and respectfully request early, favorable action on the application. Should the Examiner believe that an interview would advance the prosecution of this application, the Applicants invite him to contact the undersigned at 908.231.3444.

Respectfully submitted,



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